NATIONAL PHARMACEUTICAL ALLIANCE
SUITE 222 • 421 KING STREET • ALEXANDRIA, VIRGINIA 22314 • (703) 836-8816 • FAX (703) 549-4749 • EMAIL: NPA@EROLS.COM

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

August 27, 1999

Docket # 99D 0529

Gentlemen:

Attached are two copies of the National Pharmaceutical Alliance's Technical Committee's comments on the draft Guidance for Industry; Changes to an Approved NDA or AND. Today is the closing date for comments. We appreciate the opportunity to comment.

Very truly yours,

Robert A. Jenssi for

Christina Sizemore
President

99D-0529

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Comments by the National Pharmaceutical Alliance's Technical Committee on FDA's Guidance for Industry; Changes to an Approved NDA or ANDA. Docket No. 99D-0529, Closing Date for Comments August 27, 1999

GENERAL COMMENTS

The phrase "the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product" is used to assess change but the last part of this phrase can be interpreted two ways; first that if there is no change, the safety and effectiveness are unchanged or second, effectiveness and safety data must be collected to show no change. This should be explained/revised, etc.

This guidance directs the burden of managing change at the holder of the NDA or ANDA. There continues to be no vehicle for gaining approval of changes to DMF's for drug substances manufactured by another company.

The guidance classifies changes as major, moderate, or minor, a classification that is always open to interpretation by FDA. Thus, firms incur risk any time a change is considered other than a major one. Many firms are reluctant to accept that risk and, therefore, are reluctant to initiate change, particularly when the change involves a drug substance made under a DMF by another party. Perhaps a better characterization of these terms is warranted. The word "potential" is used to characterize each area of change. One could argue that there is always a "potential" for something to occur; it's the probability of it occurring that is critical.

Lines 32-36 indicate that where inconsistencies between this draft document and other finalized, published guidances such as the SUPACs, the latter will be superseded by this guidance. This seems odd since it is known that the agency is now rewriting SUPAC-IR. Additionally, in at least two places (see our comments under V. Components and Composition and under VI. Sites lines 248-252) the present draft guidance seems to escalate former SUPAC-IR requirements. Additionally, lines 191-194 add confusion to the relationship of this guidance to previously issued guidances. The issuance of this guidance within the next several months without any SUPAC revisions completed will cause confusion in the post approval change process.

Although this is a general guidance, in at least five places it gives the recommendation to consult with the appropriate CDER review staff or division. All attempts should be made to eliminate these references since they will introduce the likely probability of receiving different advice depending on what review staff or division is consulted.

SPECIFIC COMMENTS

II. Reporting Categories

Moderate change uses the word "moderate" to define it (line 57). We recommend that it be replaced with "on average some" to describe its potential to have an adverse effect.

Lines 64-68 indicate that if FDA informs the applicant within 30 days that required information is missing which the firm must submit, there is not time limitation after the information is provided to the agency. Shouldn't there be another 30 day window in which FDA must respond so the firm may institute the change?

Minor change uses the word "minimal" to describe it (line 75). We recommend that the phrase "little or no potential" replace it to describe the possibility of an adverse event.

IV. Assessing the Effect of Manufacturing Changes

A. Validate the Effects of the Change (line 105, 111, Footnote 5). We recommend to change the term "Validate the Effect of the Change" to use the word "assess" which is used in parenthesis to explain the word "validating" on line 111. By changing the term FDA would eliminate any confusion between the meaning in relation to cGMP validation studies. This would eliminate the need for Footnote 5 and would be consistent with the "assess" language used elsewhere in the guidance.

C. Adverse Effect (lines 167-181) is subject to different interpretations. As an example, a manufacturing change to increase tablet hardness may slow dissolution marginally but remain within specification. Is this to be judged adverse? If it is judged adverse, then a distinction between an adverse effect and an adverse impact needs to be made.

V. Components and Composition

Lines 187-189 state that changes in qualitative or quantitative formulation are major changes *unless exempted by regulation or guidance*. This seems to say that Section III, Components and Composition of SUPAC-IR which allows certain Level 1 and 2 excipient changes prevails over this guidance. However, this contradicts what is said in lines 32-34 as to the priority of this guidance over prior published guidances. This needs to be cleared up especially since lines 191-194 state that a CBE or annual report change may be covered in one or more guidances describing post-approval changes. This is all terribly confusing and needs clear, concise and specific language instead of the universal statement that appear in lines 32-34.

VI. Sites

Under A. General Considerations, lines 200-201 sites are said to include containers, closures and components sites yet these facilities are almost never inspected by FDA. Therefore, lines 248-252 would seem to make any site change for a package component be a prior approval supplement. In our opinion these type of changes should be

reportable in an annual report.

The phrase "type of operation" (lines 212-216) is used several times. It should be defined since it is crucial in describing what may or not be submitted as a changes being effected supplement. It does seem to be a change from the language in the current regulation for a change to a new facility for a drug substance. Present 314.70(c)(3) states that the manufacturing process at the new facility must not "differ materially" from that at the old facility and that the new facility has received a satisfactory cGMP inspection within the previous two years covering "that manufacturing process". Strictly interpreted, the same manufacturing process had to be inspected as that used in the original plant. This was often difficult to achieve and some firms and possibly some investigators interpreted this to mean a more general process i.e. synthesis of any drug substance rather than a specific synthesis of a specific drug substance.

If FDA is easing up on the possible strict interpretation of the present 314.70(c)(3), then it is to be congratulated but so that all (including field investigators) are on the same wavelength, the phrase "type of operation" should be defined. If FDA is not modifying the strict interpretation of 314.70(c)(3), then we recommend that it should.

Under B. Major Changes (Prior Approval Supplement) (lines 248-252) #1. needs better definition in the case of restarting an operation. Certainly, an operation that is restarted after many years is substantially different than a restarted process wherein the time frame might only be a few months. Suppose a firm is presently manufacturing in the U. S. and wants to move a manufacturing operation to Puerto Rico. Under SUPAC-IR the firm could do this via a CBE supplement. If the firm gives up production in the U. S. as part of the Puerto Rico supplement and then decides 6 or 12 months later that it wants to use the U. S. facility again for the same drug, it would need to provide a prior approval supplement for the change under this guidance. That just doesn't make sense. Additionally, if the firm got the Puerto Rico facility as an alternate facility and didn't use the U. S. one for a time, would start up at the U. S. facility again require a supplement even though it is still an approved facility to manufacture the drug?

Under B. Major Changes (Prior Approval Supplement) line 259 re changes that could affect contamination or cross contamination. Almost all manufacturing site refurbishing theoretically (potentially) could affect contamination/cross contamination either to improve it or to alter HVAC systems in some manner. This should be rewritten to apply only where the refurbishing does affect conditions in an adverse manner or where major changes in the contamination prevention have occurred. Consideration should be given that prior approval be applicable only to antibiotic and potent drug/cytotoxic handling facilities. In our opinion. much of facility refurbishment should be reclassified to annual reporting or to no reporting. As currently practiced, compliance has the responsibility of determining suitability of facilities as well as monitoring any facility/refurbishment, a practice that seems to be working.

Under B. Major Changes (Prior Approval Supplement) # 5. and # 6. (lines 271-279) we have two comments. #5. states that transfer of an aseptically processed sterile drug substance or drug product to a newly constructed, refurbished or different processing facility is an example of a Major Change and would require a pre-approval supplement. #5. does not distinguish between a different plant or within an existing facility and we take this to mean that it is for both. However, we recommend that FDA reconsider this point since moving an aseptic operation from one building to another on the same campus is much less risky than moving to an entirely different campus. This is due for several reasons including trained personnel at the same facility, the same seasonal variation in the microbiological background at the same facility and the same water quality. Thus, we recommend that this type of change be placed in C. Moderate Changes # 1.b.

For # 6. we recommend removal of "5" from this section since 5. involves aseptic processing.

VII. Manufacturing Process

A. General Considerations states (lines 346-353) that actually no matter what a firm may do, when there is substantial *potential* for adverse effects regardless if there has been no effect, the change should be filed in a prior approved supplement. This seems to refute the notion previously expressed a number of times by the agency that regulations and guidances should be based on good science and scientific principles. Thus this seems to be saying that a prior approval supplement should be submitted just in case something unexpected shows up and it will make reviewers feel comfortable.

B. Major Changes (Prior Approval Supplements) 1. Changes that may affect the controlled-release (lines 366 - 369) of a solid oral dosage form. The addition of a code imprint by embossing, debossing, or engraving on a modified release solid oral dosage form should be classified as a minor change, and therefore be included in an Annual Report. Any change in surface area to the solid dosage form would be so small as not to effectively change the release rate of the active ingredient. If such a small change would significantly affect the release rate, the product has other release issues that would need to be resolved separately from any embossing issue.

B. Major Changes (Prior Approval Supplements) 5. lists as a major change " any process change made after the final intermediate processing step in drug substance manufacture" (lines 416-417). This seems to preclude a different result that may be contained in BACPAC II. Shouldn't this statement wait until BACPAC II is issued or is it effectively stating what will be contained in BACPAC II?

B. Major Changes (Prior Approval Supplement) appears to include a redundancy in B. 4. and 5. (lines 414 and 418-420). The former lists as a major change "Change in the route of synthesis of a drug substance" while the latter lists "Changes in the synthesis or

manufacture of the drug substance that may affect its impurity profile ----". Aren't these the same?

B. Major Changes (Prior Approval Supplement) it is recommended that the sentence in lines 421-423 have the word "list" added at the end. This addition would clarify the meaning intended by the agency.

C. Moderate Changes (Supplement-Changes Being Effected in 30 days) redefinition of an intermediate, excluding the final intermediate, as a starting material (lines 466-467). Why would this need a supplement at all rather than an annual report as long as the new designated starting material has the same specifications as the intermediate.

C. Moderate Changes (Supplement-Changes Being Effected) lines 431-432 uses the phrase "except as otherwise noted". Does this phrase refer to the examples listed under B. Major Changes? Please clarify in the final guidance.

C. Moderate Changes (Supplement-Changes Being Effected) no changes have been identified by the agency (line 475). This seems odd since the proposed revision of 314.70 section IV. E. states that "based on FDA's experience, certain changes may be implemented when FDA receives the supplement ---". Does FDA's experience not include minor changes in the manufacturing process that may be placed into effect immediately upon submission of a supplement? Right now repetition of a manufacturing step is not considered a rework procedure and, therefore, does not require a supplement. This may be done to further reduce the water content of a blend when the test values indicate that the water content, although within specifications, is getting close to the upper limit. We propose that increasing or decreasing drying time by up to ±10% should be a change that may be placed into effect immediately.

D. Moderate Changes (Annual Report) lines 481-482 uses the phrase "except as otherwise noted". Does this phrase refer to the examples given under B. Major Changes and C. Moderate Changes? Please clarify in the final guidance.

D. Minor Changes (Annual Report) lines 485-487 we recommend adding the word "list" to the end of the sentence. This change will clarify the meaning intended by the agency.

D. Minor Changes (Annual Report) we recommend that the phrase "other than a modified release dosage form" be deleted from line 489 to reflect that a change in embossing for a modified release solid oral dosage form is also a minor change that may be reported in an annual report.

VIII. Specifications

A. General Considerations

Specification and acceptance criteria are defined in lines 496-497 and 500-501 respectively. However, these terms should be deleted from this section since they are defined in the Glossary of Terms.

B. Major Changes (Prior Approval Supplement) 3. for a new regulatory analytical procedure (line 519). This should be modified to add "for non-compendial drug products" since if it is a change in a USP monograph, it becomes a change made to comply with an official compendium which is covered under D. Annual Reports.

C. Moderate Changes (Supplement-Changes Being Effected) 2.b., c. and d. (lines 540-556) refer to criteria and test procedures that are almost always conducted by raw material manufacturers and firms do not typically know what they are, let alone if they are being changed. Unless these were specified in the DMF, the drug product firm would not get notified.

C. Moderate Changes (Supplement-Changes Being Effected) 2.a. (lines 558-562), it is recommended that this entire section be deleted and reclassified as a minor change to be reported in an annual report. Any addition/change of a specification, procedure, etc. to "provide increased assurance" that the drug is safe and effective will not have a moderate potential to have an adverse effect on the safety and effectiveness of a drug product. By using the phrase "provide increased assurance", FDA is automatically classifying the change as minor, not moderate.

D. Minor Changes (Annual Report) 1. lines 567-571 lists any change made to comply with an official compendium but then adds the caveat that the change must "provide the same or greater level of assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application." If a test method or specification is changed in a USP monograph, that then becomes the official test method or specification for that drug product whether or not the change provides the same or greater level of assurance. The caveat is a contradictory and irrational proposal which will lead to many discordant situations, a few of which will be described herein.

1. In this very guidance it is stated that "The analytical procedures in the *U.S. Pharmacopeia/National Formulary* (USP/NF) are those legally recognized under section 501(b) of the Act as the regulatory analytical procedures for compendial items. ----- For purposes of determining compliance with the Act, the regulatory analytical procedure is used." Thus, when a change occurs in as USP monograph, whether or not it provides the same level or greater assurance, a firm is required by law to change to it and use it. FDA must approve the change or cause a firm to be in regulatory violation.

2. When a USP change results in a firm not being able to meet the requirements of the change, FDA is sympathetic to a firm's plight but still insists that it must eventually meet

the revision.

3. FDA has a compendial monograph staff that should be able to work out any differences with the USP over changes that do not give the same or greater levels of assurance before a revised monograph becomes official.

4. If FDA refuses to approve USP changes in test procedures as a result of official monograph changes it leaves itself open to having two standards for the same drug product. This can occur when Drug A has, for example, three approved ANDAs using the old monograph and FDA refuses to approve changes in the revised monograph for these old products but must approve any subsequently submitted ANDAs using the revised monograph since the revised monograph is the only one now existing.

IX. Package

A. General Considerations. It is recommended that deleting the sentences beginning with "CDER considers the following packaging changes ----" to the end of the paragraph (lines 596-606). The examples given are specifically listed under B. Major Changes are repetitious and are not needed here.

D. Minor Changes (Annual Report) 2. lines 661-662 reserves a change in container size and/or shape to containers containing the same number of dose unit for a non-sterile dosage form. We recommend that non-sterile liquids be added to this section when the container change is to a smaller container containing the same number of dose units and that the latter be removed from C. Moderate Changes (Supplement-Changes Being Effected) c. lines 651-652.

Glossary of Terms

Acceptance Criteria (line 807) used the work "criteria" to define criteria. Replace "criteria" in the definition with "standards".

Validate the Effects of the Change (line 869) . Recommend that the word "Validate" be replaced by the word "Assess" because the usual meaning of validate is not meant here. Then replace the word "assess' in the definition with the word "evaluate". These changes will eliminate confusion around the term "validate".

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